

Negative Pressure Wound Therapy as a Drug Delivery System

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**The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board**

Title: Negative Pressure Wound Therapy as a Drug Delivery System

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Sponsor: American Diabetes Association

1. Introduction and Purpose:

The aim of this study is to improve wound healing in high risk diabetic patients that require surgical debridement or open amputation for an infected foot wound. The most common reason for hospitalization and amputation amongst people with diabetes is an infected foot wound. **Negative Pressure Wound Therapy (NPWT) [1, 2] has dramatically changed the outcomes of complex wounds, especially in the diabetic foot.** Compared to standard wound care, diabetic patients treated with NPWT are 1.4 times more likely to heal and 2.5 times less likely to require amputation [2-4]. Our preliminary work suggests that using irrigation with NPWT provides an additional dramatic improvement in healing compared to “traditional NPWT”. NPWT with irrigation is analogous to the benefit of drug-eluting stents compared to bare metal stents for cardiovascular disease [5, 6]. Irrigation increases the effectiveness of NPWT by reducing bacterial load, accelerating wound healing, and decreasing the cost of wound treatment [7-11]. Thus, the combination of NPWT and irrigation solution could significantly improve clinical outcomes and reduce the economic burden in this seriously ill population.

Traditional Negative Pressure Wound Therapy delivers subatmospheric pressure to a wound using a foam dressing that is sealed with an occlusive dressing. The addition of irrigation with antiseptic solution is delivered to the sealed wound using additional tubing from an IV bag attached to the NPWT device. Our preliminary data suggest that when traditional NPWT is combined with antiseptic irrigation, there is a higher rate of wound closure, fewer surgeries, and shorter length of hospitalizations for complex infected diabetic foot wounds (Preliminary Study 2).

We propose a randomized clinical study of 151 patients with infected, diabetic foot wounds that require hospitalization. Hospital patients with surgical diabetic foot wounds will be randomized to receive NPWT with polyhexanide irrigation or “conventional” NPWT with no irrigation.

Aim 1: Compare clinical outcomes with Negative Pressure Wound Therapy with irrigation and Negative Pressure Wound Therapy without irrigation. We expect that patients treated with NPWT with irrigation will have higher proportions of wounds that heal, fewer surgeries, and faster wound healing trajectories when compared to patients treated with traditional NPWT without irrigation.

Aim 2: Compare quantitative cultures and clinical infections in patients treated with NPWT with irrigation compared to conventional NPWT. We hypothesize that patients

treated with NPWT and irrigation will have a significantly lower bacterial load, and fewer and less severe clinical infections.

Aim 3: Compare health function and well-being of patients treated with NPWT with irrigation compared to conventional NPWT. We hypothesize that patients treated with NPWT and continuous irrigation will have significantly higher indicators of functional health and well-being as compared with standard NPWT.

2. Background:

There is a worldwide epidemic of diabetes. According to data from the World Health Organization, the world prevalence of diabetes among adults was 6.4% in 2010, affecting 285 million people worldwide. The prevalence of diabetes is expected increase to 7.7% by 2030 (439 million adults).[12] The U.S. Centers for Disease Control and Prevention estimate that 26 million people in the US have diabetes.[13] Over the past five years in the United States, the prevalence of diabetes has increased 26% and the cost has increased 41% to \$245 billion a year [14, 15].

Diabetic Foot Wounds and Amputations: Diabetic foot wounds are common, complex and costly.[16-18] One of the most frequent causes of hospitalization among persons with diabetes is an infected foot wound.[13] In the United States in 2007, approximately one-quarter of the total cost of diabetes treatment was spent on lower extremity complications (\$43.5 billion). [19-21] The incidence of diabetic foot ulcers in Medicare enrollees is about 7% [22, 23], and approximately 61% of foot wounds become infected. Twenty-percent of patients with infected foot wounds end up with amputation of the foot or leg.[16] The incidence of lower extremity amputation is 0.5-1.0% (90,000 per year). The annual mortality rate for diabetics with foot ulcers is about 11%, and after a lower extremity amputation, mortality is nearly 22%.[14, 24-32] [17, 33-39]

Negative Pressure Wound Therapy (NPWT) has dramatically changed the care of complex diabetic foot wounds. Compared to standard wound care, patients treated with NPWT are 1.4 times more likely to heal and 2.5 times less likely to require amputation.[40] [2-4]

NPWT is used extensively to treat infected wounds. Experimental studies in pigs demonstrated a reduction in quantitative cultures from 10^8 to 10^6 colony forming units with NPWT [41, 42] However in clinical trials “traditional NPWT” has not been shown to reduce the risk of infection. For instance, Armstrong and Lavery reported that 16.9% of NPWT patients were treated for infection compared to 9.4% of patients that received “standard of care” in a randomized clinical trial (RCT) of diabetic foot wounds. The addition of antiseptic irrigation provides a significant reduction in bacterial load compared to “traditional NPWT” (**Preliminary Work: Study 2**). We expect it will translate into fewer clinical infections [11], fewer surgeries and faster wound healing.

SIGNIFICANCE OF NEW INTERVENTION We will use NPWT with irrigation as a drug delivery system. This application is analogous to the benefit of drug-eluting stents compared to bare metal stents for cardiovascular disease [5, 6]. We believe delivering topical medications to the wound bed will dramatically improve wound healing, reduce infections and reduce amputations. Our preliminary work has shown that irrigation reduces bacterial load significantly more than NPWT alone (**Preliminary Work: Study 3**) [11]. In addition a higher

proportion of patients treated with NPWT and irrigation had their wounds surgically closed, required fewer surgeries, and shorter hospitalizations (**Preliminary Work: Study 2**).

Irrigation Solution Selection: There are many potential irrigation products to decrease bacteria in wounds. Povidone iodine, Dakin's solution, silver nitrate, and polyhexanide are effective to eliminate bacteria. However, some of these have been shown to damage fibroblasts and are thought to impede healing. Irrigation with Polyhexanide solution (PHMB) seems to be the best choice to treat infected diabetic foot wounds because it is a very effective antiseptic, and it promotes wound healing. Polyhexanide, marketed under the names Prontosan and Lavasept, is polyhexamethylene biguanide (PHMB). It is a strong base and interacts with acidic phospholipids in the cell membrane, leading to increased permeability and cell death.[43] PHMB has a broad antimicrobial spectrum, including Gram-positive and Gram-negative bacteria, and biofilm-forming organisms.[44] A >5 log 10 reduction after 5 minutes of application is achieved with 0.02% polyhexanide against *S. aureus*, *E. coli*, *E. faecium*, *P. aeruginosa* and *C.albicans*.[45]

Polyhexanide Improves Wound Healing: Several studies indicate that PHMB solution and gel improve wound healing. Kramer [47] compared PHMB and octenidine and Ringer's lactate solution in superficial 20 mm diameter wounds in pigs (n=108 wounds). There were no differences in histology or tissue compatibility in the treatment groups. There was faster wound healing in PHMB animals compared to the other treatments (PMHB 22.9 vs. Ringers 24.1 and octemidine 28.3 days, p<0.05). Schmit-Neuerburg conducted a double-blinded RCT in contaminated wounds and compared 0.2% PHMB (n=45) and Ringers lactate solution (n=35). The PHMB group had better wound healing and faster reduction of Gram positive infections.[46] Valenzuela [48] evaluated PHMB in a RCT in chronic wounds (n=142). They compared "standard of care" to 0.1% PHMB gel. Patients in the PHMB groups demonstrated reversal of positive cultures (p=0.004), decreased surface area (p=0.013), and increased granulated tissue (p=0.001) compared to standard of care treatments.

Polyhexanide Irrigation with NPWT: Several retrospective studies have used Polyhexanide irrigation with NPWT compared to patients treated standard wound care.[7-10] Timmers reported the results of a retrospective study of 30 patients with osteomyelitis of the pelvis or lower extremity that received NPWT with PHMB irrigation compared to 90 patients that received standard of care. The PHMB irrigation subjects had fewer recurrent infection (10% vs. 59%, p<0.001), Hospital stay 36 (15-75) vs. 73 days (6-149) p<0.001, and fewer surgical procedures 2 (range: 1-4) vs. 5 (range: 2-42) p<0.001.

INNOVATIONS:

1. NPWT as a drug delivery system. NPWT has dramatically changed wound care in the last 10 years. Our initial focus is to deliver antiseptic solution to the wound bed to reduce the bacterial load and accelerate wound healing. In the future, we plan to use the same approach to deliver growth factors and anti-inflammatory medications to wounds. Our preliminary data suggests that when "traditional" NPWT is combined with irrigation, there is a synergistic effect. A higher proportion of wounds are closed with fewer surgeries in the operating room and shorter hospital stays. This is the first Clinical Effectiveness Research study that compares clinical and economic outcomes with NPWT and NPWT with irrigation. This is the first NPWT RCT in infected diabetic wounds. Figure 2, above shows simultaneous irrigation with NPWT. Irrigation solution is directed to the wound through IV tubing. It flows across the

wound bed and then is collected through a separate suction system that also maintains constant pressure of 125 mm Hg on the wound bed.

2. Determine the effect of NPWT and NPWT with continuous irrigation on serial quantitative bacterial cultures and clinical infections: This is the first study to evaluate serial tissue cultures in infected diabetic foot wounds to evaluate (1) the effect of NPWT on bacterial load and (2) the role of bacterial load on wound healing. Our results may help redefine “infection” as it pertains to wound healing in persons with diabetes and as a pivotal factor in wound failure.

3. Selection Bias: Industry sponsored research routinely excludes high-risk patients with significant PAD, poor glucose control and co-morbidities, even though the excluded population is often the population that needs advanced wound therapies the most. The industry sponsored RCTs previously referenced systematically excluded high-risk patients with moderate peripheral artery disease (PAD) (ABI <0.70), glycated hemoglobin >10%, active infection, and end stage renal disease requiring dialysis [49].

4. Dropouts: Dropouts are common in wound studies (20-35%) and are categorized as failures in intent-to-treat studies. With their consent, we will continue to follow patients that elect to drop out or whose physicians believe it is in their best interest to stop participation. We will continue to see them and evaluate their wound and document any adverse events. To our knowledge, no studies in the wound healing literature have been designed to follow subjects that elect to drop out. We will document their treatments, but no protocol-specific treatments will be provided once they withdraw from the active treatment phase. This will allow us to estimate adherence effectiveness, as well as intent-to-treat.

C. PRELIMINARY DATA

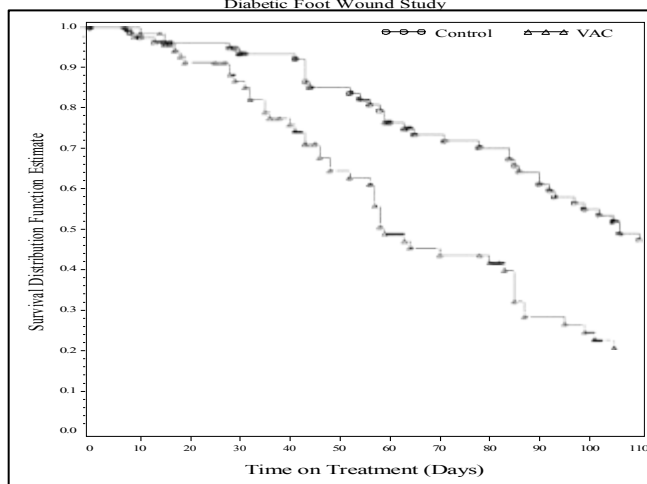
Preliminary Studies: Drs. Lavery’s team has completed several NPWT studies [3, 26, 34, 40, 50-54] to support this research. They have used investigator initiated, industry funding from KCI, ITI, Convatec, Smith Nephew and Thermotek to execute preliminary animal and human studies to gather preliminary NPWT data.

Our Preliminary Work with NPWT indicates:

1. NPWT patients have a higher proportion of wounds that heal compared to “standard wound care” [1, 4, 53]. **(Preliminary Work: Study 1)**
2. NPWT is less expensive than “standard wound care” in diabetic foot wounds [54].
3. NPWT with irrigation provides a higher proportion of wound closure, fewer surgeries and shorter length of hospitalization in diabetic foot wounds. **(Preliminary Work: Study 2)**
4. NPWT with irrigation with polyhexanide biguanide (PHMB) significantly reduces *Pseudomonas aeruginosa* compared to “traditional NPWT” in a swine model. **(Preliminary Work: Study 3)**
5. There is no difference in wound healing in diabetic foot wounds treated with high (125 mm Hg) and low (75mm Hg) continuous pressure. **(Preliminary Work: Study 4)**

Study 1: Negative Pressure Wound Therapy After Partial Diabetic Foot Amputation: a Multicentre, Randomised Controlled Trial. The Lancet, 2005[40]

Kaplan-Meier Estimates for Duration on Randomized Treatment (Days)
Protocol VAC2001-07
Diabetic Foot Wound Study



This study demonstrated that NPWT is superior to “standard wound care” to heal complex diabetic foot wounds. We enrolled 162 patients into a 16-week, randomized clinical trial. Inclusion criteria consisted of diabetic patients with partial foot amputation wounds. Patients were randomly assigned to NPWT (n=77) or standard moist wound care (n=85). The treating physician had discretion regarding the level (80-200 mm Hg) and mode of pressure (continuous or intermittent). More patients healed in the NPWT group than in the control group

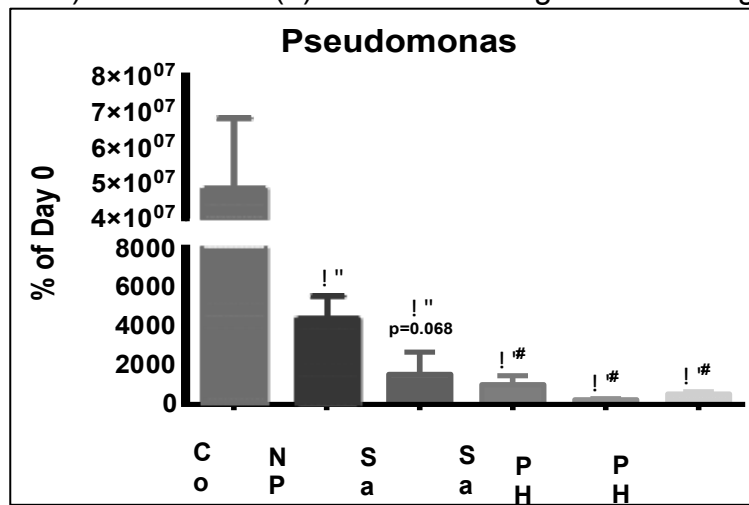
56% vs. 39%, p=0.04). Recurrent infection was higher in the NPWT group (NPWT 16.9% vs. 9.4%), but the difference was not statistically significant.

Kaplan Meier Analysis: The survival analysis shows a significant difference in the time to healing. The median time to wound closure was 59 days for patients in the NPWT group and 106 days for controls.

Study 2: The Impact of Negative Pressure Wound Therapy with Instillation Compared to Negative Pressure Wound Therapy. Plast Reconstr Surg 2013 This study shows that NPWT with two different doses of Prontosan irrigation solution decreases the number of surgeries, length of hospitalization, and increases the proportion of wounds that are closed compared to “traditional NPWT”. We conducted a retrospective study of hospitalized patients with infected lower extremity wounds that received NPWT without irrigation (n=74), NPWT with irrigation with polyhexanide biguanide (PHMB) for 6 minutes every hour (n=34), and NPWT with irrigation with polyhexanide biguanide (PHMB) for 20 minutes every hour (n=34). The proportion of wounds that were surgically closed was significantly higher, and the number of surgeries was significantly less in patients that received NPWT with 6 minutes of irrigation compared to standard NPWT without irrigation. Similar trends were seen with NPWT with 20 minutes of irrigation.

Table 1	NPWT n=74	NPWT 6 minute irrigation n=34	NPWT 20 minute irrigation n=34
Number of Surgeries	3.0 ± 0.9	2.4 ± 0.9 p=0.04	2.6 ± 0.9 p=0.003
Length of Stay (days)	14.9 ± 9.2	11.9 ± 7.8 p=0.10	11.4 ± 5.1 p=0.03
Time to Final Surgical Procedure	9.23 ± 5.2	7.8 ± 5.2 p=0.04	7.5 ± 3.1 p=0.002
Percent Closed	62%	94% p<0.001	80% p=0.08

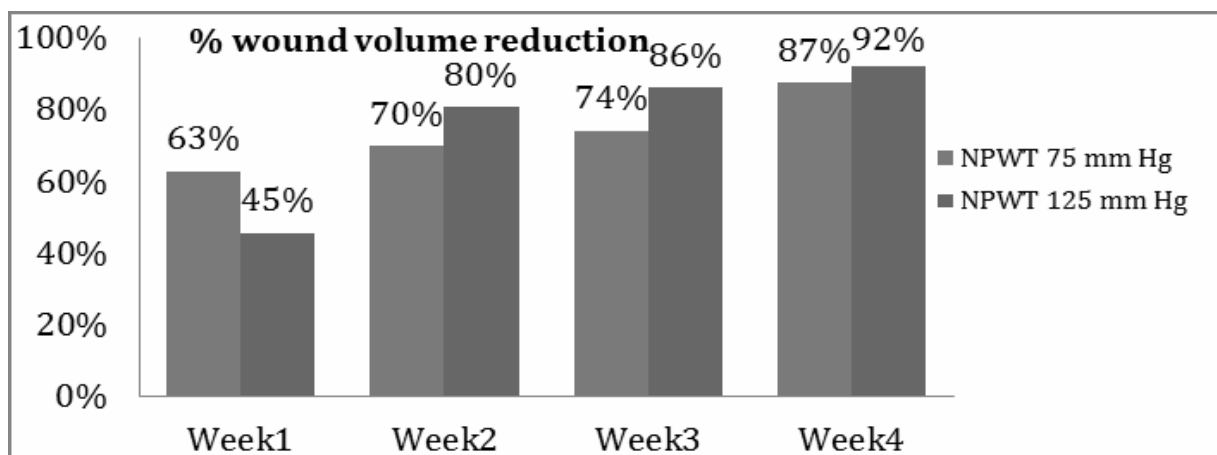
Study 3: Simultaneous irrigation and negative pressure wound therapy enhances wound healing and reduces wound bioburden in a porcine model. Wound Repair Regen 2013. The objective of the study was to compare wound healing and reduction in pseudomonas on acute wound using a swine model. We evaluated six wound treatments (1.) control wound (2.) NPWT 125 mm Hg continuous pressure with foam interface (3.) NPWT with low volume irrigation (15 cc/hr) with Saline (4.) NPWT with low volume irrigation (15 cc/hr) with 1% polyhexanide biguanide (PHMB) (5) NPWT with high volume irrigation (40 cc/hr) with Saline (6) NPWT with high volume irrigation (40 cc/hr) with 1% PHMB. Each



wound was inoculated with ~500 CFU of *Pseudomonas aeruginosa*, packed with saline-moistened gauze and covered with Tegaderm. After 3 days post inoculation, dressings were removed; wounds were treated for 21 days with dressing changes twice a week. With Control treatment, *Pseudomonas aeruginosa* bioburden increased $\sim 5 \times 10^7$ over the 21-day time course. This proliferation was substantially reduced with the application of NPWT or NPWT with irrigation, except for low flow rate

treatment with saline ($p=0.068$). There was a significant and sustained reduction in wound area reduction in NPWT wounds compared to control wounds over the duration of the study ($p<0.05$). There was no difference in wound area reduction among the NPWT and NPWT with irrigation groups in healthy young pigs.

Study 4: Randomized Clinical Trial to Compare Negative Pressure Wound Therapy Approaches with Low and High Pressure, Silicone-Coated Dressing and Polyurethane Foam Dressings. Plast Reconstr Surg 2013 This RCT demonstrates that wound volume reduction is the same in patients treated with high (125 mm hg) and low (75 mm Hg) NPWT. We evaluated 40 patients in a 4-week RCT. This study compared a low pressure NPWT device using 75 mm Hg continuous pressure with a silicone coated gauze interface (Convatec, NJ) and the “standard of care approach” using 125 mm Hg continuous pressure with a sponge interface (KCI San Antonio, TX). There was no difference in the percent wound volume reduction at 4 weeks (87% vs. 92%), or the proportion of wounds with complete closure (50% for 75 mm Hg vs. 60% for 125 mm Hg). Wound closure was achieved with split thickness skin grafts, rotational flaps or delayed primary closure. No wounds healed by secondary intention during the 4 week evaluation period. NPWT using 125 mm Hg pressure with a foam interface and 75 mm Hg pressure with silicone coated gauze interface had almost identical wound healing outcomes.



3. Concise Summary of Project:

Study Design: We plan a randomized clinical trial of 151 patients with infected diabetes-related lower extremity wounds to compare the clinical and economic effectiveness of negative pressure wound therapy with continuous irrigation and negative pressure wound therapy without irrigation.

Rationale for Treatment Groups

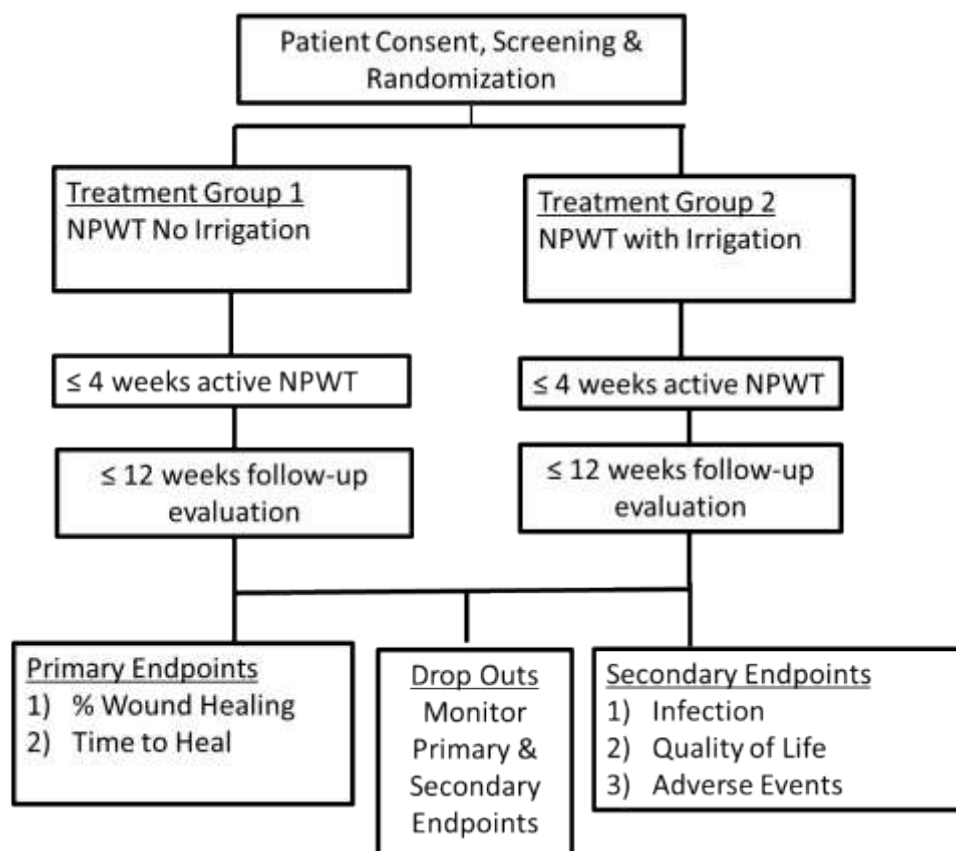
(1.) Treatment Group 1 Standard NPWT: We chose 125 mm Hg constant pressure with polyurethane foam because this is one of the most common setting used in clinical practice and reported in clinical studies with diabetic foot wounds (**Preliminary Work: Studies 1-4**).

(2.) Treatment Group 2 (NPWT with continuous irrigation): Constant pressure therapy from 125 mm Hg will be used. However, we will program the NPWT device to provide continuous irrigation at a rate of 40 cc/hour. This rate is based on findings from our preliminary work (**Preliminary Work: Study 3**).

Table 2 NPWT Operating Characteristics of Comparative Devices		
Pressure	125 mm Hg continuous pressure	125 mm Hg continuous pressure
Irrigation	None	1% Polyhexanide irrigation 40 cc/hour
Interface	Polyurethane Foam	Polyurethane Foam

Population and Recruitment: We will enroll 151 patients from two centers: The University of Texas Southwestern University Hospital and Parkland Hospital over the period of three years.. We will screen and enroll patients with wounds in the inpatient setting. Patients will be randomized to receive traditional NPWT or NPWT with continuous irrigation while they are hospitalized. The average hospitalization for patients that receive NPWT is 13.3 days. Patients that do not have their wound surgically closed during hospitalization will be discharged with negative pressure wound therapy without irrigation. After discharge from the hospital, subjects will be seen twice weekly by home health, and we will evaluate subjects in

clinic during routine post-operative visits up to a total of 16-week period or until 30 days after the wound heals. A study flow chart is provided below.



NOTE: Subjects who continue on NPWT after hospital discharge will receive NPWT without irrigation for home use

4. Study Procedures:

Screening Procedures

- Review and sign the Informed Consent and HIPAA Authorization
- The study doctor will review the inclusion and exclusion criteria
- Demographics (such as age, gender, race or ethnicity)
- Collection of Sitting blood pressure and pulse at admission
- Collection of Height and weight at admission
- Collection of the medical and surgical history
- Collection of the history of the wound
- Wound assessment(s) – wound etiology, wound history, location of study wound and infection assessment
- Hyperspectral imaging within 30 days of screening
- Vascular/Neurological evaluation - we will do various tests and measurements to assess the sensation (feeling) and circulation (blood flow) in the subject's feet and

lower legs. To assess the sensation, we will do a monofilament sensory test and a vibration threshold perception test on the study foot. We will calculate the neuropathy disability score of both feet. To assess circulation, we will record Skin Perfusion Pressures in the study foot using a Sensilase System (Väsamed, Eden Prairie, MN) within 30 days of screening. We will calculate the ankle brachial index (ABI) at screening and collect available arterial doppler data from the medical record within 6 months of screening. None of these tests are invasive (using needles), uncomfortable or have risks greater than standard care.

- Results of standard-of-care laboratory tests including a white blood cell count, blood chemistry (tests to see how well organs, such as the liver and kidneys are working), glycated hemoglobin, albumin, prealbumin, erythrocyte sedimentation rate, C-reactive protein and blood glucose. Results of a serum pregnancy test (standard care for women of child-bearing potential as part of pre-op labs) will also be collected. Collection of a list of the subject's current antibiotics
- We will provide the SF-36 Questionnaire and other patient-reported outcomes

questionnaires and collect them while subjects are inpatient.

This visit will last about 2 hours.

If the subject qualifies for the study, they will participate in the following procedures:

Group Assignment

If the researchers believe the subject can take part in this study, s/he will be assigned randomly (like a flip of a coin) to receive one of the following therapies:

- **Negative Pressure Wound Therapy with Irrigation**
- **Negative Pressure Wound Therapy without Irrigation**

The group is assigned randomly (like flipping a coin). The sponsor or researchers do not know in advance what group assignment each subject will receive. Neither the subject nor the researchers will be allowed to choose which group s/he is assigned to.

Study Intervention

The subject will receive either:

- **Quantum™ +Simultaneous Irrigation (NPWTi) – Negative Pressure Wound Therapy with Prontosan® , or**
- **Quantum™ (NPWT) –Negative Pressure Wound Therapy (without Prontosan®)**

Assigned therapy will continue in the hospital until the physician determines that the wound is ready for closure. If the subject's wound is healing, study therapy will be discontinued and standard dressings will be applied. If surgical closure is needed, the subject will return to the Operating Room for a procedure to close the wound.

If the wound is not ready for closure during the hospital stay, subjects will continue NPWT at home. NPWT at home will be without irrigation.

Procedures and Evaluations during the Research

The study therapy will only be given while the subject is in the hospital. If the subject's wound is not ready for closure during the hospital stay, the subject will continue NPWT at home. NPWT at home will be without irrigation.. Once the therapy is stopped s/he will continue to be followed by the study doctor. After the subject is released from the hospital s/he will need to see the study doctor during regular post-operative visits. The study doctor will continue to check the wound. If the wound closes, s/he will see the study doctor 30 days later to have the closed wound checked.

Day of First Surgery:

- 3D images after the surgery with eKare Insight device
- Tissue and bone samples – the doctor will take 2 small samples of tissue from the subject's wound before debridement (removal of dead or unhealthy tissue), and after debridement (clean margins) and 1 sample of bone before debridement in case of bone infection, and these tissue samples will be kept and tested for the amount and type of bacteria that are present (qPCR analysis/laboratory analysis).
- Wound measurements after the surgery
- The study doctor will decide if the subject still qualifies to be in the study
- Randomization (like flipping a coin) to either **Quantum™** NPWT with Irrigation or **Quantum™** NPWT without Irrigation
- Placement of therapy on the wound
- Collection of current antibiotics
- Collection of adverse event information (any changes in health)

Daily Treatments (while in the hospital):

- Collection of current antibiotics
- Collection of adverse event information

This will take about 15 minutes.

Additional Surgery (if needed to remove dead tissue/bone or to close the wound):

- Tissue sample – the doctor will take 2 small samples of tissue from the subject's wound after debridement (clean margin), and these tissue samples will be kept and tested for the amount and type of bacteria that are present (qPCR analysis/laboratory analysis)
- 3D images of the wound after the surgery/debridement at bedside with eKare Insight device if the wound is still open.
- Wound measurements after the surgery/debridement at bedside
- Wound closure or placement of therapy on the wound
- Collect current antibiotics
- Collect adverse event information

If the subject's wound is not closed upon hospital discharge, NPWT will continue at home without irrigation.

Home Health Visits

If the subject continues to receive NPWT after hospital discharge, the subject will be seen twice weekly by a home health nurse for dressing changes. The home health nurse will collect sitting blood pressure and pulse rate. Amount, type and character of wound drainage will be documented, as well as any adverse events and changes to concomitant medications. Offloading will be reapplied after dressing changes.

Follow-Up Visits per standard of care (after therapy has stopped):

- Dressing change / removal/ Offloading
- Wound measurements and infection assessment

- Results of standard-of-care laboratory tests including a white blood cell count, blood chemistry (tests to see how well organs, such as the liver and kidneys are working), glycated hemoglobin, albumin, prealbumin, erythrocyte sedimentation rate, C-reactive protein and blood glucose.
- 3D image of the wound with eKare device (if indicated, if the wound is still open)
- Collection of current antibiotics
- Collection of adverse event information

These visits will take about 30 minutes.

End of Study - Wound Closure Follow-up Visit (after the wound closes, if it closes within 16 weeks from Day of First Surgery) or Week 16:

- Closed wound assessment
- For subjects whose wound has not closed:
 - 3D images of the wound with eKare device
 - Return to standard care
- Collection of current antibiotics
- Collection of adverse event information
- SF-36 Questionnaire and other patient-reported outcomes questionnaires

This visit will take about 30 minutes.

5. Sub-Study Procedures:

N/A

6. Criteria for Inclusion of Subjects:

Diagnosis of diabetes mellitus
Men/women ≥ 21 years old
Post-operative foot or ankle wounds sized > 5 cm
ABI ≥ 0.5 or toe pressures >30 mmHg

7. Criteria for Exclusion of Subjects:

Active Charcot arthropathy
Unable to use NPWT at home
Untreated bone or soft tissue infection
Unable to keep research appointments

Active alcohol (> 14 drinks per week over the last 3 months) or substance abuse (current use of cocaine, heroine or methamphetamine or if drug or alcohol use will interfere with follow up visits in foot clinic in the opinion of the investigator)

8. Sources of Research Material:

The Researchers will collect demographics (age, gender, ethnic origin), medical history; medications; results of laboratory testing including pregnancy testing, operative reports, results of study tests and procedures, vital signs, height and weight, examinations and images of the wound, off-loading, results of analysis of tissue samples, adverse events and treatment and information about the costs of the subject's healthcare.

9. Recruitment Methods and Consenting Process:

Subjects will be identified by the PI or Sub-I's from the investigators' patients scheduled for surgery.

The PI, Sub-I, or study coordinator will carefully review this research study with the subject and any family members or caregivers. Any questions will be answered, and it will be emphasized that participation in the research is voluntary. When all questions are answered, and the subject has agreed to participation in the research, the subject will sign the Consent and HIPAA Authorization. The subject will receive copies of the signed documents.

Since this is a study that is initiated during an inpatient stay, the research study procedures and activities will be reviewed with the patient and any friend or family member who may also participate in the consent interview. Adequate time will be provided to read the consent, and any questions will be answered. It will be emphasized that participation in the study is voluntary, and that a decision not to participate will not affect the care that the subject will receive.

10. Potential Risks:

Quantum™ NPWT and Quantum™ NPWTTherapy with Irrigation:

- Skin and tissue reaction or allergic reaction
- Mild pain or discomfort
- Bleeding
- Slowing of the heart beat (vagal response, bradycardia)
- Lung compromise
- Study solution accidentally entering a body cavity
- Infection at the wound
- Autonomic dysreflexia (in patients with spinal cord injuries)
- Foam left in the wound
- Difficulty moving around because of the weight and attachment to the therapy unit
- Possible entanglement or tripping on tubing or electrical cords attached to the therapy unit
- Incorrect programming of therapy unit
- Creating tunnels in the wound bed
- Delayed healing of the wound
- Worsening of the condition of the wound
- Severe allergic reaction
- Burn from therapy unit or electrical cord malfunction

The FDA has issued a warning about bleeding and infection. In the past two years, FDA received six death and 77 injury reports associated with NPWT devices. Most deaths occurred at home or in a long-term care facility. Bleeding was the most serious complication, with reports of bleeding associated with six deaths and 17 injuries. Patients with bleeding required emergency room visits and/or hospitalization and were treated with surgery and blood transfusions.

Of the 83 reports to FDA, 27 reports indicated worsening infection from original open infected wounds or from pieces of dressing that remained in the wound, and 32 reports noted injury from foam dressing pieces and foam sticking to tissues or clinging to the wound. Most of these patients required surgery, additional hospitalization, and antibiotics.

These rare, but serious complications of NPWT will be monitored for while subjects are in the hospital and at study visits to the clinic.

Prontosan® Wound Irrigation Solution:

- Skin sensitivity or allergic reaction
- Severe allergic reaction

Prontosan® is a wound cleansing solution. Polyhexamethylene biguanide (PHMB), a product contained in Prontosan® is suspected to cause cancer in laboratory or animal studies, but there is no definite data connection with humans. These findings are linked to the use of PHMB in a higher concentration than the amount contained in Prontosan.

Additional potential risks include Loss of Confidentiality; Risks to Embryo, Fetus or Breast-fed Infant and Other Risks which may be unknown at this time.

11. Subject Safety and Data Monitoring:

The principal investigator will monitor the experience of the subjects at least monthly and the conduct of the protocol, including:

- Study accrual rate
- Experience of study participants
- Study attrition including participant withdrawals/dropouts
- Patterns of AEs and/or unanticipated events
- Patterns of protocol deviations and/or violations
- Changes in risk/benefit

We will also employ a study monitoring committee which will include Drs. La Fontaine and Lavery, as well as our team statistician and study coordinator. We plan to meet once a month to discuss the progress of the study. We will also install a data safety monitoring board to review the data of the study on an annual basis. We will also use this forum to discuss specific issues and decisions that may arise during the implementation of the study.

12. . Procedures to Maintain Confidentiality:

All study visits and procedures will be conducted in the patient's room at Parkland Hospital or in the private treatment rooms at the Parkland Foot Wound Clinic.

Subjects will be assigned a unique Subject Number upon consent. All study documents and specimens will contain this number and no unique identifying information. The subject number will be used on all data and samples that leave campus. No personal identifying information will be included.

Hard copy data (source files) will be kept separately in the locked coordinator's office. The link between the subject's name and the subject number will be kept in a password-protected computer file with access limited to members of the research team.

Electronic data will be password protected with access limited to members of the research team in the departmental 'R' drive.

No identified data will leave the campus.

13. Potential Benefits:

There may or may not be direct benefits to the subject from participation in this research. **Quantum™** NPWT or **Quantum™** NPWT with Irrigation may help to heal the wound, but this cannot be guaranteed.

However, results of this research may contribute new information that will help and benefit other people who have surgically debrided wounds in the future. Information gained from this research could lead to better treatment.

14. Biostatistics:

Sample Size: In a preliminary study, the proportion of subjects with closed wound was 62% using traditional NPWT and 94% using NPWT with irrigation (**Preliminary Work: Study 3**). For the sample size, we used a more conservative estimate of wound closure and estimated 80% wound closure with NPWT with irrigation. Using a two-sided Chi-square with alpha of 1.5 and 80% power and a 20% drop out rate, a sample size of 70 subjects per group (total of 151) is required with 62% healing in NPWT group and 80% in the NPWT with irrigation treatment group.

Analysis Plan: We will examine the descriptive statistics, frequency distribution and graphic plots of each variable to detect the data errors, outlying values, number and pattern of missing data and normality of distributions. The natural log transformation will be applied to variables which are highly skewed. Baseline characteristics of study population will be presented as means (standard deviation) for continuous variables with normal distribution, median (inter-quartile ranges) for continuous variables with high skewed distribution or proportion for categorical variables according to the treatment groups. The difference in means between treatment groups will be compared using the two-sample t-test. The difference in distribution will be compared using Wilcoxon rank-sum test. The difference in percentage treatment groups will be compared using the Chi-square test.

Study Population:

- Intention-to-Treat (ITT) Population: The ITT population will include all randomized subjects who at least received one treatment and had at least one post-baseline efficacy assessment. The ITT population will be used for the primary efficacy analysis.

- Per Protocol Population (PP): The PP population will consist of subjects in the ITT population who did not have major protocol violations. The review of protocol violations will be performed and signed off prior to study database lock and unblinding. The primary efficacy analysis and secondary analyses will be conducted on the PP population as part of a sensitivity analysis.
- Safety Population: The Safety population will include all subjects who received treatment. The safety population will be used for the safety analysis.

Missing Data Imputation: For the primary outcomes with ITT analysis, we will use multiple imputation procedure to impute the missing data. The sensitivity analysis will be performed to evaluate the effect of assumption of imputation. For the secondary outcomes and safety analysis, missing data will not be imputed.

Multiplicity: Stepwise Holm's test will be used to adjust for the multiple comparisons.

References

1. Armstrong, D.G. and L.A. Lavery, *Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial*. Lancet, 2005. **366**(9498): p. 1704-10.
2. Blume, P.A., et al., *Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial*. Diabetes Care, 2008. **31**(4): p. 631-6.
3. Lavery, L.A., et al., *Prediction of healing for postoperative diabetic foot wounds based on early wound area progression*. Diabetes Care, 2008. **31**(1): p. 26-9.
4. Lavery, L.A., et al., *A comparison of diabetic foot ulcer outcomes using negative pressure wound therapy versus historical standard of care*. Int Wound J, 2007. **4**(2): p. 103-13.
5. Moussa, I., et al., *Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRollmUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy*. Circulation, 2004. **109**(19): p. 2273-8.
6. van Domburg, R.T., et al., *The impact of the introduction of drug-eluting stents on the clinical practice of surgical and percutaneous treatment of coronary artery disease*. Eur Heart J, 2005. **26**(7): p. 675-81.
7. Timmers, M.S., et al., *Negative pressure wound treatment with polyvinyl alcohol foam and polyhexanide antiseptic solution instillation in posttraumatic osteomyelitis*. Wound Repair Regen, 2009. **17**(2): p. 278-86.
8. Zelen, C.M., et al., *A prospective study of negative pressure wound therapy with integrated irrigation for the treatment of diabetic foot ulcers*. Eplasty, 2011. **11**: p. e5.
9. Schintler, M.V.P., E. C.; Kreuzwirt, G.; Grohmann, M. R.; Spendel, S.; Schamagl, E. , *The impact of V.A.C. Instill® in severe soft tissue infections and necrotizing fasciitis*. Infection. Infection 2009, 2009. **37**: p. No Supplement 1 pp 31-36.
10. B, L., *application of VAC instill therapy in case of periprosthetic infection in hip arthroplasty*. Infection Arthroplasty Infection, 2009. **37**: p. 13-17.
11. Davis, K., et al., *Simultaneous irrigation and negative pressure wound therapy enhances wound healing and reduces wound bioburden in a porcine model*. Wound Repair Regen, 2013.
12. *World Diabetes Atlas*, 2011, International Diabetes Federation: Brussels.
13. CDC. *National diabetes fact sheet*. 2007 [cited 2010 May 31, 2010]; Available from: www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.
14. Driver, V.R., et al., *The costs of diabetic foot: the economic case for the limb salvage team*. J Am Podiatr Med Assoc, 2010. **100**(5): p. 335-41.
15. American Diabetes, A., *Economic costs of diabetes in the U.S. in 2012*. Diabetes Care, 2013. **36**(4): p. 1033-46.

16. Singh, N., D.G. Armstrong, and B.A. Lipsky, *Preventing foot ulcers in patients with diabetes*. JAMA, 2005. **293**(2): p. 217-28.
17. Lavery, L.A., et al., *Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort*. Diabetes Care, 2003. **26**(5): p. 1435-8.
18. Armstrong, D.G., L.A. Lavery, and R.P. Wunderlich, *Risk factors for diabetic foot ulceration: a logical approach to treatment*. J Wound Ostomy Continence Nurs, 1998. **25**(3): p. 123-8.
19. Driver, V.R., et al., *The costs of diabetic foot: the economic case for the limb salvage team*. Journal of the American Podiatric Medical Association, 2010. **100**(5): p. 335-41.
20. Rogers, L.C., L.A. Lavery, and D.G. Armstrong, *The Right To Bear Legs: An Amendment to Healthcare. How Preventing Amputations Can Save Billions for the US Health-care System* J Amer Podiatr Med Assn, 2008. **98**(2): p. In Press.
21. Armstrong, D.G., et al., *Choosing a Practical Screening Instrument to Identify Patients at Risk for Diabetic Foot Ulceration*. Archives of Internal Medicine, 1998. **158**: p. 289-292.
22. Lavery, L.A., et al., *Re-evaluating How We Classify the Diabetic Foot: Restructuring the International Working Group's Diabetic Foot Risk Classification*. Diabetes Care, 2007.
23. Lavery, L.A., et al., *Diabetic Foot Syndrome: Evaluating the Prevalence and Incidence of Foot Pathology in Mexican Americans and non-Hispanic Whites from a Diabetes Disease Management Cohort*. Diabetes Care, 2003. **26**: p. 1435-1438.
24. Armstrong, D.G., *Discussion. Update on negative-pressure wound therapy*. Plastic and Reconstructive Surgery, 2011. **127 Suppl 1**: p. 116S.
25. Armstrong, D.G., et al., *It's Not What You Put on, but What You Take Off: Techniques for Debriding and Off-Loading the Diabetic Foot Wound*. Clinical Infectious Diseases, 2004. **39 Suppl 2**: p. S92-S99.
26. Armstrong, D.G. and L.A. Lavery, *Decreasing foot pressures while implementing topical negative pressure (vacuum-assisted closure) therapy*. Int J Low Extrem Wounds, 2004. **3**(1): p. 12-5.
27. Jeffcoate, W.J., P. Price, and K.G. Harding, *Wound healing and treatments for people with diabetic foot ulcers*. Diabetes Metab Res Rev, 2004. **20 Suppl 1**: p. S78-89.
28. Jeffcoate, W.J. and K.G. Harding, *Diabetic foot ulcers*. Lancet, 2003. **361**(9368): p. 1545-51.
29. Armstrong, D.G., et al., *Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial*. Diabetes Care, 2005. **28**(3): p. 551-4.
30. Jeffcoate, W.J., et al., *Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes*. Health technology assessment, 2009. **13**(54): p. 1-86, iii-iv.
31. Ulbrecht, J.S., P.R. Cavanagh, and G.M. Caputo, *Foot problems in diabetes: an overview*. Clin Infect Dis, 2004. **39 Suppl 2**: p. S73-82.
32. Margolis, D.J., et al., *Prevalence of Diabetes, Diabetic Foot Ulcer, and Lower Extremity Amputation Among Medicare Beneficiaries, 2006 to 2008: Data Points #1*, in *Data Points Publication Series*. 2011: Rockville (MD).
33. Lavery, L.A., et al., *Risk factors for foot infections in individuals with diabetes*. Diabetes Care, 2006. **29**(6): p. 1288-93.
34. Lavery, L.A., et al., *Validation of the Infectious Diseases Society of America's diabetic foot infection classification system*. Clin Infect Dis, 2007. **44**(4): p. 562-5.
35. Izumi, Y., et al., *Mortality of first-time amputees in diabetics: a 10-year observation*. Diabetes Res Clin Pract, 2009. **83**(1): p. 126-31.
36. Lavery, L.A., et al., *Risk factors for developing osteomyelitis in patients with diabetic foot wounds*. Diabetes Res Clin Pract, 2009. **83**(3): p. 347-52.
37. Ndip, A., L.A. Lavery, and A.J. Boulton, *Diabetic foot disease in people with advanced nephropathy and those on renal dialysis*. Curr Diab Rep, 2010. **10**(4): p. 283-90.
38. Lefebvre, K.M. and L.A. Lavery, *Disparities in amputations in minorities*. Clin Orthop Relat Res, 2011. **469**(7): p. 1941-50.
39. Lavery, L.A., et al., *Amputations and foot-related hospitalisations disproportionately affect dialysis patients*. Int Wound J, 2013.

40. Armstrong, D.G. and L.A. Lavery, *Negative Pressure Wound After Partial Diabetic Foot Amputation: a Multicentre, Randomised controlled trial*. The Lancet, 2005. **366**: p. 1704-1710.
41. Morykwas, M.J., et al., *Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation*. Ann Plast Surg, 1997. **38**(6): p. 553-62.
42. Ngo, Q.D., K. Vickery, and A.K. Deva, *The effect of topical negative pressure on wound biofilms using an in vitro wound model*. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society, 2012. **20**(1): p. 83-90.
43. Ikeda, T., et al., *Interaction of a polymeric biguanide biocide with phospholipid membranes*. Biochim Biophys Acta, 1984. **769**(1): p. 57-66.
44. Rosin, M., et al., *Effect of a polyhexamethylene biguanide mouthrinse on bacterial counts and plaque*. J Clin Periodontol, 2001. **28**(12): p. 1121-6.
45. Muller, G. and A. Kramer, *Biocompatibility index of antiseptic agents by parallel assessment of antimicrobial activity and cellular cytotoxicity*. J Antimicrob Chemother, 2008. **61**(6): p. 1281-7.
46. Hubner, N.O. and A. Kramer, *Review on the efficacy, safety and clinical applications of polyhexanide, a modern wound antiseptic*. Skin Pharmacol Physiol, 2010. **23 Suppl**: p. 17-27.
47. Kramer, A., et al., *Influence of the antiseptic agents polyhexanide and octenidine on FL cells and on healing of experimental superficial aseptic wounds in piglets. A double-blind, randomised, stratified, controlled, parallel-group study*. Skin Pharmacol Physiol, 2004. **17**(3): p. 141-6.
48. Valenzuela, A.R. and N.S. Perucho, *[The effectiveness of a 0.1% polyhexanide gel]*. Rev Enferm, 2008. **31**(4): p. 7-12.
49. McCallon, S.K., et al., *Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds*. Ostomy Wound Manage, 2000. **46**(8): p. 28-32, 34.
50. Armstrong, D.G., et al., *Validation of a diabetic foot surgery classification*. Int Wound J, 2006. **3**(3): p. 240-6.
51. Armstrong, D.G., L.A. Lavery, and L.B. Harkless, *Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation [see comments]*. Diabetes Care, 1998. **21**(5): p. 855-9.
52. Andros, G., et al., *Consensus statement on negative pressure wound therapy (V.A.C. Therapy) for the management of diabetic foot wounds*. Ostomy Wound Manage, 2006. **Suppl**: p. 1-32.
53. Armstrong, D.G., L.A. Lavery, and A.J. Boulton, *Negative pressure wound therapy via vacuum-assisted closure following partial foot amputation: what is the role of wound chronicity?* Int Wound J, 2007. **4**(1): p. 79-86.
54. Apelqvist, J., et al., *Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds*. Am J Surg, 2008. **195**(6): p. 782-8.
55. Wunderlich, R.P., et al., *Reliability of digital videometry and acetate tracing in measuring the surface area of cutaneous wounds*. Diabetes Res Clin Pract, 2000. **49**(2-3): p. 87-92.
56. Davis, K.E., et al., *Validation of a laser-assisted wound measurement device for measuring wound volume*. J Diabetes Sci Technol, 2013. **7**(5): p. 1161-6.
57. *Diagnosis and classification of diabetes mellitus*. Diabetes Care, 2010. **33 Suppl 1**: p. S62-9.
58. Castronuovo, J.J., Jr., et al., *Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia*. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, 1997. **26**(4): p. 629-37.
59. Yamada, T., et al., *Clinical reliability and utility of skin perfusion pressure measurement in ischemic limbs--comparison with other noninvasive diagnostic methods*. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, 2008. **47**(2): p. 318-23.
60. Castronuovo, J.J., Jr., et al., *Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia*. J Vasc Surg, 1997. **26**(4): p. 629-37.

61. Yamada, T., et al., *Clinical reliability and utility of skin perfusion pressure measurement in ischemic limbs--comparison with other noninvasive diagnostic methods*. J Vasc Surg, 2008. **47**(2): p. 318-23.
62. Diamond, J.E., et al., *Reliability of a diabetic foot evaluation*. Phys Ther, 1989. **69**: p. 797-802.
63. Lavery, L.A., et al., *Accuracy and durability of Semmes-Weinstein monofilaments: What is the useful service life?* Diabetes Res Clin Pract, 2012.
64. Caselli, A., et al., *Validation of the nerve axon reflex for the assessment of small nerve fibre dysfunction*. Journal of neurology, neurosurgery, and psychiatry, 2006. **77**(8): p. 927-32.
65. Abbott, C.A., et al., *The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort*. Diabet Med, 2002. **19**(5): p. 377-84.
66. Lipsky, B.A., et al., *Specific guidelines for the treatment of diabetic foot infections 2011*. Diabetes Metab Res Rev, 2012. **28 Suppl 1**: p. 234-5.
67. Lipsky, B.A., et al., *Expert opinion on the management of infections in the diabetic foot*. Diabetes Metab Res Rev, 2012. **28 Suppl 1**: p. 163-78.
68. Peters, E.J., et al., *A systematic review of the effectiveness of interventions in the management of infection in the diabetic foot*. Diabetes Metab Res Rev, 2012. **28 Suppl 1**: p. 142-62.
69. Lipsky, B.A., et al., *Specific guidelines for the treatment of diabetic foot infections 2011*. Diabetes/metabolism research and reviews, 2012. **28 Suppl 1**: p. 234-5.
70. Bendy, R.H., Jr., et al., *Relationship of Quantitative Wound Bacterial Counts to Healing of Decubiti: Effect of Topical Gentamicin*. Antimicrobial agents and chemotherapy, 1964. **10**: p. 147-55.
71. Robson, M.C. and J.P. Heggers, *Bacterial quantification of open wounds*. Mil Med, 1969. **134**(1): p. 19-24.
72. Xu, L., et al., *Bacterial load predicts healing rate in neuropathic diabetic foot ulcers*. Diabetes Care, 2007. **30**(2): p. 378-80.
73. Lipsky, B.A., et al., *Diagnosis and treatment of diabetic foot infections*. Clin Infect Dis, 2004. **39**(7): p. 885-910.
74. Dowd, S.E., et al., *Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP)*. PLoS One, 2008. **3**(10): p. e3326.
75. Willrich, A., et al., *Health related quality of life, cognitive function, and depression in diabetic patients with foot ulcer or amputation. A preliminary study*. Foot Ankle Int, 2005. **26**(2): p. 128-34.
76. Peters, E.J., L.A. Lavery, and D.G. Armstrong, *Diabetic lower extremity infection: influence of physical, psychological, and social factors*. J Diabetes Complications, 2005. **19**(2): p. 107-12.
77. Armstrong, D.G., et al., *Quality of life in healing diabetic wounds: does the end justify the means?* J Foot Ankle Surg, 2008. **47**(4): p. 278-82.
78. Peters, E.J., et al., *Functional status of persons with diabetes-related lower-extremity amputations*. Diabetes Care, 2001. **24**(10): p. 1799-804.
79. Vileikyte, L., et al., *Diabetic peripheral neuropathy and depressive symptoms: the association revisited*. Diabetes Care, 2005. **28**(10): p. 2378-83.
80. Goodridge, D., E. Trepman, and J.M. Embil, *Health-related quality of life in diabetic patients with foot ulcers: literature review*. J Wound Ostomy Continence Nurs, 2005. **32**(6): p. 368-77.
81. Engelberg, R., et al., *Musculoskeletal function assessment: reference values for patient and non-patient samples*. J Orthop Res, 1999. **17**(1): p. 101-9.
82. Engelberg, R., et al., *Musculoskeletal Function Assessment instrument: criterion and construct validity*. J Orthop Res, 1996. **14**(2): p. 182-92.
83. Price, P. and K. Harding, *Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb*. Int Wound J, 2004. **1**(1): p. 10-7.
84. Lavery, L.A., et al., *The "Probe to Bone" Test for Diagnosing Osteomyelitis of the Foot in Persons with Diabetes: Reliable, or Relic?* Diabetes, 2005. **54 (Suppl1)**: p. 65(OR).

85. Lavery, L.A., et al., *Risk Factors for Foot Infections in Persons with Diabetes Mellitus*. Diabetes Care, 2006. **29**: p. 1288-1293.
86. Lavery, L.A., et al., *Predictive Value of Foot Pressure Assessment as Part of a Population-Based Diabetes Disease Management Program*. Diabetes Care, 2003. **26**: p. 1069-1073.

Protocol Activity	Screening	Baseline Day 0 – Day of Surgery	Week 1 Inpatient (may continue into Week 2)**	Home Health Visits Weeks 2-4	Week s 2-15 ASC	End of Study- after wound closure or Week 16
Informed Consent	X					
Demographics and Medical/Surgical History	X					
Collected Sitting blood pressure & pulse rate	X			X		
Inclusion/Exclusion Criteria	X					
History of the wound	X					
Collected Weight/Height	X					
Blood testing - Standard of care	X				X	
Vascular/Neurological Evaluation	X					
Wound imaging (eKare device) if the wound is						
		X	X		X	X
Hyperspectral imaging (within 30 days of screening)	X					
Wound Assessment	X	X	X	X	X	X
Tissue and bone samples for qPCR cultures & bioburden analysis – obtained during surgery or routine debridement		X	X (in case of additional surgery)			
NPWT/NWPT (i) randomization and therapy placement/dressing application/changes		X (initial application post-op per Investigator/ WOCN)*	X	X	X	
SF-36 Questionnaire & other patient-reported outcomes questionnaires	X***					X
Offloading			X	X	X	X
Adverse Events		X	X	X	X	X
Current antibiotics	X	X	X		X	X

* At bedside, NPWT or NPWT(i) for ≤4 weeks

** Week 1 inpatient includes procedures done at bedside and/or if the patient returns to the OR for additional surgery and discharge from the hospital.

*** Obtained while subject is in patient